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(54) Title: NOVEL CSAIDS

(57) Abstract

The novel compounds of formulas (I) and (II), bicyclo 5,6-Dihydro-7*H*-pyrrolo-[1,2-a]-imidazol-7-ol and 7-one substituted ring systems, have been found to be useful inhibitors of the 5-lipoxygenase and cyclooxygenase enzymes, and cytokine suppressive agents, respectively, and therefore useful in the treatment and prophylaxis of disease states mediated thereby.

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TITLE
NOVEL CSAIDS

FIELD OF THE INVENTION

This invention relates to the novel compounds of Formula (I), pharmaceutical compositions and various methods of use of the compounds of Formulas (I) - (III).

BACKGROUND OF THE INVENTION

The cyclooxygenase (CO) mediated pathway oxidizes arachidonic acid to produce PGH_2 which is in turn metabolized to the prostanoids (PGE_2, TxA_2, and prostacyclin). These products are produced by various cells including polymorpho-nuclear leukocytes, mast cells and monocytes. The 5-lipoxygenase (5-LO) mediated pathway oxidizes arachidonic acid initially to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) which is further metabolized to LTA_4, the precursor to the peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) and LTB_4. Additionally 5-HPETE is converted to 5-hydroxyeicosatetraenoic acid (5-HETE).

The arachidonic acid oxygenated products, as noted above, have been identified as mediators of various inflammatory conditions. The various inflammatory disease states caused by these mediators and many other conditions, as discussed herein, are all conditions in which a dual inhibitor of both CO and 5-LO would be indicated.

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs (hereinafter CSAID's), i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6 and TNF; and compounds which are also capable of inhibiting the oxygenation of arachidonic acid by inhibition of enzymes such as lipoxygenase, specifically 5-lipoxygenase (5-LO) and cyclooxygenase (CO) thereby preventing the formation of various leukotrienes and prostaglandins.

SUMMARY OF THE INVENTION

This invention relates to a method of treating an oxygenated polyunsaturated fatty acid mediated disease (hereinafter OPUFA) in an animal in need thereof which comprises administering to such animal, an effective amount of a compound of Formula (I).

This invention also relates to a method of treating a cytokine mediated disease, in an animal in need thereof, which comprises administering to such animal an effective amount of a compound of Formula (II) or (III).

This invention specifically relates to a method of inhibiting the production of interleukin-1 (hereinafter IL-1) in an animal in need thereof which comprises administering to such animal an effective amount of a compound of Formula (II) or (III) sufficient to inhibit IL-1. More specifically the inhibition of the production of IL-1 is useful in the treatment, prophylactically or therapeutically, of any disease state in a mammal which is exacerbated or caused by excessive or unregulated IL-1 production.

This invention specifically relates to a method of inhibiting the production of Tumor Necrosis Factor (hereinafter TNF) in an animal in need thereof which comprises administering to such animal, an effective amount of a compound of Formula (II) or (III) sufficient to inhibit TNF. More specifically the inhibition of the production of TNF is useful in the treatment, prophylactically or therapeutically, of any disease state in a mammal which is exacerbated or caused by excessive or unregulated TNF production.

The compounds of Formulas (I) to (III) have been found to be useful in inhibiting the enzymes involved in the oxygenation of polyunsaturated fatty acid metabolism and the compounds of Formulas (II) and (III) have been found to be useful in inhibiting cytokines.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

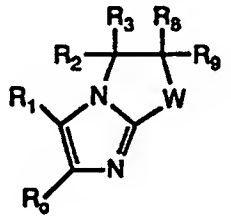
The compounds of Formula (II) or (III) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in vivo. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (II), or (III). Such viruses include, but are not limited to; HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I).

The compounds of Formula (II) and (III) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

A preferred method of this invention is the treatment, therapeutically or prophylactically, of viral infections, in particular where such viruses are sensitive to upregulation by TNF or IL-1 will elicit TNF or IL-1 production in vivo by administering an effective amount of a compound of Formula (II) or (III) or most preferably, the compound is 5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol or 5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol. or the pharmaceutically acceptable salts thereof.

The compounds of Formula (I) are represented by the structure:



(I)

wherein

W is -(CR_4R_5)-, or -(CR_4R_5)-(CR_6R_7)- ;

R_4 and R_5 together are oxo; or one of R_4 and R_5 is OH and the other of R_4 and R_5 is hydrogen;

R_2, R_3, R_6, R_7, R_8, and R_9 are hydrogen; or one or two of R_2, R_3, R_6, R_7, R_8 and R_9 are independently hydrogen or C_{1-2}alkyl;

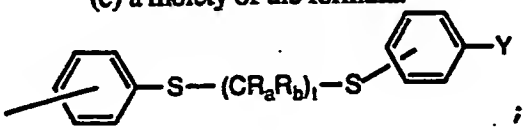
one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl; and the other of R_1 and R_0 is

(a) phenyl;

(b) mono- or di-substituted phenyl wherein the substituents are selected,independently, from C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, aryloxy, heteroaryloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 2-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} 2-alkenyl-1-sulfinyl, arylthio, arylsulfinyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3}alkanamido),

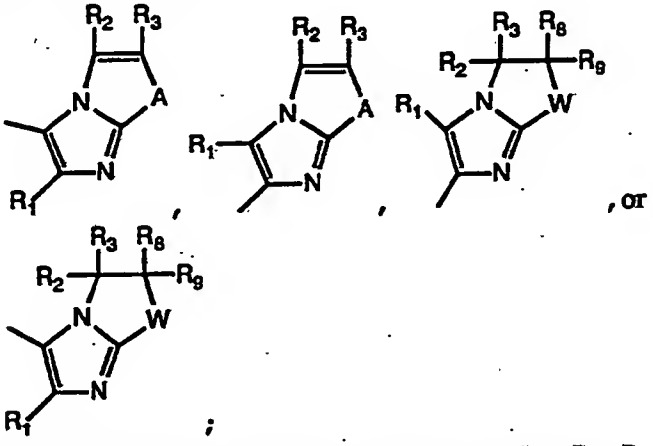
N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, acyloxyalkylsulfinyl, acyloxyalkylthio or Z; or

(c) a moiety of the formula:



;

wherein Y is selected from



, or

;

wherein t is 0 or 1; W and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined above;

A is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_a and R_b are independently selected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;

Z is $-S-(CR_aR_b)_t-S-Z_1$;

Z_1 is a functional moiety;

provided that

a) when R_1 is 4-pyridyl,W_1 is $-(CR_4R_5)-$, then R_0 is other than a 4-methoxy substituted phenyl;

b) when R_0 is pyridyl or C_{1-4}alkyl-4-pyridyl then R_1 is a phenyl substituted with other than a N-(C_{1-3} alkyl) alkanamido, or N-(C_{1-3} alkanamido);

or a pharmaceutically acceptable salt thereof.

Preferred mono-substitution of the compounds of Formula (I) are C_{1-4} alkyl, C_{1-4} alkyl $S(O)_m$, m is 0 or 1; C_{1-4} alkoxy,halo, N-(C_{1-3} alkyl) alkanamido, or N-(C_{1-3} alkanamido).

Preferred di-substitution of the phenyl ring for compounds of Formula (I) are:

(a) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-4} alkoxy, halo, or C_{1-4} alkyl;

(b) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl or CF_3, and the other substituent is C_{1-3} alkylamino, N- (C_{1-3}alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, amino, N-pyrrolidino or N-piperidino, thiol, alkylsulfinyl, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxy-carbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, acyloxyalkylthio or Z; or

(c) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, acyloxyalkylthio, acyloxyalkylsulfinyl or Z; or

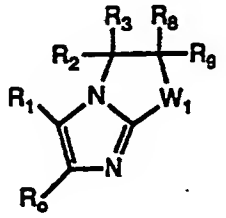
(d) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-4} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, C_{1-3} alkylthio, C_{1-3} alkyl-sulfonyl, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxy-carbonylthio, alkoxythionothio,arylthio, arylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio, or Z.

A particularly preferred group of compounds are the subgenus of compounds of Formula (I), wherein R_1 is 4-pyridyl or Cl-4 alkyl-4-pyridyl; and R_0 is a monosubstituted phenyl wherein said substituents are selected from C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or halo. This preferred group of compounds are also useful in the treatment of cytokine mediated diseases.

Particularly preferred compounds of Formula (I) those wherein W is -(CR_4R_5)-. More preferred are those compounds wherein the phenyl substituent is in the para position.

Most preferred is where the C_{1-4} alkyl moiety of the R_1 term C_{1-4} alkyl-4-pyridyl is in the 2-position of the pyridyl ring and is the alkyl group is methyl.

Another aspect of the present invention are the novel compounds of Formula (II). The compounds of Formula (II) are useful in the treatment of a cytokine mediated disease as well as in the treatment of OPUFA mediated diseases. The compounds of Formula (II) are represented by the structure:



(II)

wherein

W_1 is -(CR_4R_5)- ;

R_4 and R_5 together are oxo; or one of R_4 and R_5 is OH and the other is selected from H ;

R_2, R_3, R_8, and R_9 are independently hydrogen or C_{1-2} alkyl;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl provided that when R_1 or R_0 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located in the 2-position of the pyridine ring; and the other of R_1 and R_0 is

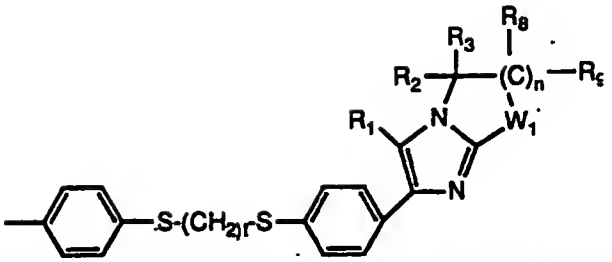
(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl or Z; or

(b) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C_{1-2} alkoxy, halo, or C_{1-4} alkyl; or

(d) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group; or

(e) monosubstituted phenyl wherein said substituent is



t is 0 or 1; W_1, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above;

provided that when R_1 is 4-pyridyl, W_1 is -(CR_4R_5)-, and one of R_4 and R_5 are OH and the other is H, or together are oxo, then R_0 is other than a 4-methoxy substituted phenyl;

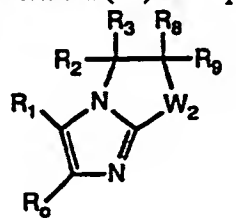
wherein Z is - S-S - Z_a and Z_a is a C_{1-9} alkyl or phenyl;

and the pharmaceutically acceptable salts thereof.

Preferred substitution of Formula (II) compounds are wherein R_1 is 4-pyridyl or C1-4 alkyl-4-pyridyl; and R_0 is a monosubstituted phenyl wherein said substituents are selected from C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or halo. Particularly preferred are those compounds wherein W is -(CR_4R_5)-. More preferred are those compounds wherein the phenyl substituent is in the para position. Most preferred is where the C_{1-4} alkyl moiety of the R_1 term C_{1-4} alkyl-4-pyridyl is in the 2-position of the pyridyl ring and is the alkyl group is methyl.

This invention also relates to the novel compounds of Formula (III) as represented below. The compounds of Formula (III) are also useful for the treatment of OPUFA mediated disease or for inhibiting cytokine production.

The compounds of Formula (III) are represented by the structure:



(III)

wherein

W_2 is -(CR_4R_5) or -(CR_4R_5)-(CR_6R_7)-;

R_4 and R_5 together are oxo; or one of R_4 and R_5 is OH and the other is hydrogen;

R_2, R_3, R_6, R_7, R_8, and R_9 are hydrogen; or one or two of R_2, R_3, R_6, R_7, R_8 and R_9 are independently hydrogen or C_{1-2}alkyl;

R_1 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl;

R_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-pyrrolidino, N-piperidino, 2,2,2-

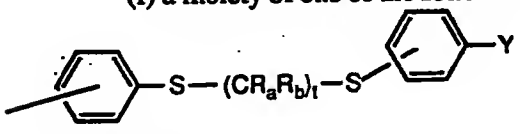
trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, acyloxyalkylsulfinyl, alkylthioalkylthio, or Z;

(b) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl or CF_3, and the other substituent is thiol, alkylsulfinyl, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, acyloxyalkylthio, acyloxyalkylsulfinyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, amino, N-pyrrolidino, N-piperidino or Z; provided that when one of the substituents is alkylsulfinyl or acyloxyalkylthio the other substituent must be CF_3 or a C_3 alkoxy; or

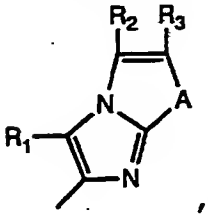
(d) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, acyloxyalkylthio, acyloxyalkylsulfinyl, or Z; or

(e) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, 2,2,2-trihaloethoxy, C_{1-3} alkylthio, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , acyloxyalkylsulfinyl, or alkylthioalkylthio; provided that when the phenyl is disubstituted with a C_3 alkoxy it is not substituted in the para position;

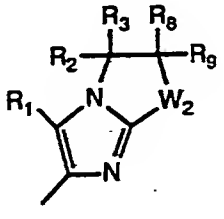
(f) a moiety of one of the following formula:



wherein Y is



, or



wherein t is 0 or 1; W_2, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined above;

A is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_a and R_b are independently selected from hydrogen, optionally substituted C_{1-9} alkyl, optionally substituted aryl, or optionally substituted heteroaryl;

Z is $-S-(CR_aR_b)_t-S-Z_1$;

Z_1 is a functional moiety;

provided that

a) when t is 0 then Z_1 is not C_{1-9} or phenyl;

b) only one of R_a and R_b can be hydrogen;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of Formula (III) those wherein W is $-(CR_4R_5)-$. More preferred are those compounds wherein the phenyl substituent is in the para position. Most preferred is where the C_{1-4} alkyl moiety of the R_1 term C_{1-4} alkyl-4-pyridyl is in the 2-position of the pyridyl ring and is the alkyl group is methyl.

Preferred R_0 substitution is C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-pyrrolidino, N-piperidino, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, alkoxyalkylthio, alkoxyalkylsulfinyl, acyloxyalkylsulfinyl, or alkylthioalkylthio.

Z_1 is a functional moiety that does not interfere with breakage of the disulfide bond in-vivo to yield the SH moiety. Z_a of Formula (II) is a subgenus of Z_1. Preferable Z_1 moieties are aryl, optionally substituted aryl, C_{1-9} alkyl, optionally substituted alkyl, heteroaryl, an optionally substituted heteroaryl, cystiene or glutathione. The optional substituents may be the same as the R_0 or R_1 phenyl moieties noted above for Formula (I).

R_a and R_b are independently selected from hydrogen, optionally substituted C_{1-9} alkyl, optionally substituted aryl, or optionally substituted heteroaryl. The optional substituents for the aryl and heteroaryl ring are the same as the R_0 and R_1 phenyl moieties noted above for Formula (I), other than Z. Preferably R_a and R_b are unsubstituted or substituted with C1-4 alkyl.

Preferred compounds of Formula (I) are:

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;

5,6-Dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol; or

5,6-Dihydro-2-(4-fluorophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol.

It should be noted that the compounds of Formula (I) where R_1 or R_0 may be a phenyl substituted with a C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} -2-alkenyl-1-sulfinyl, alkoxyalkylsulfinyl, and phenylsulfinyl moiety, may act as prodrugs which are reductively converted in vivo to the corresponding alkylthio or alkenylthio form.

It should be noted that the compounds of Formula (I) where R_1 or R_0 may be a phenyl substituted with an acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, or acyloxyalkylthio may act as prodrugs which are hydrolytically converted in vivo to the corresponding sulfhydryl form.

It should be noted that the compounds of Formula (I) where R_1 or R_0 may be a phenyl substituted with any of the disulfide moieties described herein may act as prodrugs which are oxidatively converted in vivo to the corresponding sulfhydryl form.

By the term "halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo and iodo.

By the term "C_{1-9}alkyl" or "alkyl" groups as used herein is meant to include both straight or branched chain radicals of 1 to 9 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

By the term "alkenyl" as used herein is meant to include both straight or branched chain radicals of 1 to 9 carbon atoms, unless the chain length is limited thereto, but not limited to vinyl, 1-propenyl, 2-propenyl, or 3-methyl-2-propenyl.

By the term "aryl" as used herein, in any combination, such as "aryloxy", is meant phenyl, or naphthyl.

By the term "heteroaryl" as used herein, in any combination, such as "heteroaryloxy", is meant a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S; such as, but not limited, to quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole.

By the term "sulfinyl" as used herein is meant the oxide of the corresponding sulfide. By the term "thio" as used herein is meant the sulfide. For further clarification, the following table outlines the structural attachment of the atoms of the R_1 and R_0 substituents of the compounds of Formula (I):

Table 1

R_1 or R_0 substituents	Structural Attachment
C_{1-3} alkylsulfinyl	[AS(O)-]
C_{2-5} 1-alkenyl-1-thio	[AA^1C=CHS-]
C_{2-5} 1-alkenyl-1-sulfinyl	[AA^1C=CHS(O)-]
C_{3-5} 2-alkenyl-1-thio	[ACH=CA^1CH_2S-]
C_{3-5} 2-alkenyl-1-sulfinyl	[ACH=CA^1CH_2S(O)-]
1-acyloxy-1-alkylthio	[AC(O)OCH(A^1)S-]

NOTE: A and A^1 are hydrogen or alkyl;

Table 2

Additional R_1 or R_0 Substituents	Structural Attachments:
acylthio	[DC(O)S-]
dithioacyl	[DC(S)S-]
thiocarbamyl	[DD^1NC(O)S-]
dithiocarbamyl	[DD^1NC(S)S-]
alkylcarbonylalkylthio	[DC(O)CH_2S-]
carbalkoxyalkylthio	[BOC(O)CH_2S-]
alkoxycarbonylthio	[BOC(O)S-]
alkoxythionothio	[BOC(S)S-]
alkoxyalkylthio	[BOCH_2S-]
alkoxyalkylsulfinyl	[BOCH_2S(O)]
alkylthioalkylthio	[BSCH_2S-]
disulfide [Z]	[-S(CR_aR_b)t-S-Z_1]

Note: D and D^1 are hydrogen, C_{1-9} alkyl, or phenyl; t is 0 or 1

B is C_{1-9} alkyl or aryl; R_a, R_b and Z_1 is aryl, heteroaryl or C_{1-9} alkyl (optionally substituted). The hydrogen atoms in the CH_2 groups described in Table 2 are, independently, optionally substituted by a C_{1-4} alkyl moiety.

By the term "lipoxygenase" as used herein is meant the 5-lipoxygenase, 12-lipoxygenase or 15-lipoxygenase enzymes.

By the term "inhibiting the production of IL-1" is meant

a) a decrease of excessive in vivo IL-1 levels in a human to normal levels or below normal levels by inhibition of the in vivo release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive in vivo IL-1 levels in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 as a postranslational event.

By the term "inhibiting the production of TNF" is meant

a) a decrease of excessive in vivo TNF levels in a human to normal levels or below normal levels by inhibition of the in vivo release of TNF by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the genomic level, of excessive in vivo TNF levels in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of TNF as a postranslational event.

By the term "TNF mediated disease or disease state" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease stated mediated by TNF.

By the term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of other cells, and is a molecule which modulates interactions between cells in the immune or inflammatory response. A cytokine includes, but is not limited to monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutraphils, endothelial cells, brain astrocytes, bone marrow

stromal cells, epideral keratinocytes, and ß- lymphocytes. Lymphokines are generally referred to as being produced by lymphoctye cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNFα) and Tumor Necrosis Factor beta (TNFß).

By the term "cytokine interfering or cytokine suppressive amount" is meant an effective amount of a compound of Formula (I) to (III) which will, when given for the treatment, prophylactically or therapeutically, of any disease state which is exacerbated or caused by excessive or unregulated cytokine production, cause a decrease the in vivo levels of the cytokine to normal or below normal levels.

The inhibition of a cytokine, contemplated by the present invention, for use in the treatment of a HIV-infected human, must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF-ß (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-ß are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

By the term "OPUFA mediated disease or disease state" is meant any disease state which is mediated (or modulated) by oxidation of polyunsaturated fatty acids, specifically the arachidonic acid metabolic pathway. The oxidation of arachidonic acid by such enzymes as the lipoxygenase enzymes or cyclooxgenase enzyme is specifically targeted by the present invention. Such enzymes include, but are not limited to, 5-LO, 12-LO, 15-LO, and CO; which produce the following mediators,including but not limited to, PGE_2, LTB_4, LTC_4, LTD_4, prostaglandins, thromboxane, and prostocyclin.

By the term "OPUFA interfering amount" is meant an effective amount of a compound of Formula (I) which shows a reduction of the in vivo levels of an oxgyenated arachidonic acid metabolite.

The compounds of Formula (I) - (III) may be prepared from the known intermediates of Formula (A), as shown below. The compounds of Formula (A) are known compounds and are prepared in Bender et al., U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988; Bender et al., U.S. Patent Number 4,175,127, issued November 20, 1979; Bender et al., U.S. Patent Application Serial Number 07/106,199 filed on July 10, 1987; Bender et al., U.S. Patent Number 4,803,279, issued February 9, 1989, Bender et al., U.S. Patent Number 4,719,218, issued January 12, 1988; Bender et al., U.S.

Patent Number 4,715,310, issued January 14, 1988 the entire disclosures of all of which are hereby incorporated by reference.

All of the compounds of Formula (A) may alternatively be prepared by one skilled in the art in an analogous manner readily adaptable to the present ring systems as described herein.

Compounds of Formula (A) wherein R_0 or R_1 is a phenyl substituted with a substituted disulfide moiety are prepared by mild air oxidation of the compounds of Formula (A) wherein the R or R_1 is a phenyl substituted with a sulfhydryl group. The non-symmetrical disulfides (Z) wherein Z is -S-S-Z_1 and Z_1 is aryl, heteroaryl or alkyl, the compounds may be prepared by reaction of the sulfhydryl compound with the appropriate sulfenyl halide in an ethereal solvent to afford compounds of Formula (A) wherein one of R_0 or R_1 is a phenyl substituted with one or more alkyldithio or aryl-dithio groups.

The method of Mukaiyama et al., Tetrahedron Letters, 56:5907-08 (1968) allows for use of the desired aryl-SH or alkyl-SH reagent treated with diethylazodicarboxylate in 1:1 equivalence at room temperature in a solvent, yielding an adduct which is then treated with 1:1 ratio of the mercaptan of a Formula (A) compound. This process will also yield the disulfide dimer of the compounds of Formula (A). Preferably the disulfide linkage is on the R_0 position of the compounds of Formula (A).

Compounds of Formula (A) wherein R or R_1 is phenyl substituted with an alkylthioalkylthio group are prepared by reacting the analogous sulfhydryl compound, prepared as described above, with the appropriate carbonyl component, such as formaldehyde, acetone, or acetaldehyde, using either mineral or Lewis acid catalysis conditions to yield the symmetrical dithioketal. The intermediate hydroxylalkylthio derivative reacts with another sulhydryl containing compound under the acid catalysis conditions to yield what is essentially a "bis" type compound, differing only by the alkyl chain insertion. This process produces the bis disulfide moieties of part (f) Claim 1, for instance, i.e. Formula (A)-S-CRR^1-S-Formula (A). The substitution of the alkyl, R or R^1, is determined by the reactive carbonyl functional group, wherein R or R^1 may be C_{1-9} alkyl, aryl or heteroaryl, all optionally substituted.

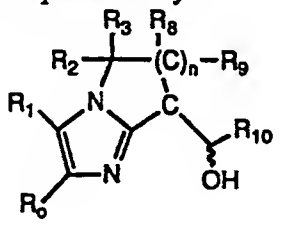
The nonsymmetrical thioketals can be prepared by the reaction of the metal mercaptan salt, prepared as described above, with a halomethyl thioether to yield compounds of Formula (A) wherein one of R or R_1 is phenyl substituted with one or more alkylthioalkylthio groups. The metal salt reacts with an independent and varying alkyl chain length halomethyl-[CRR^1]-thioalkyl[aryl/heteroaryl] compound to yield the "non-bis" type compounds, [Formula (A)-S-CRR^1-S-R^2], wherein R and R^1 are as defined above for the "bis" compounds, and R^2 is a C_{1-9} alkyl, aryl or heteroaryl group which may be optionally substituted. A mixture of R_0 and R_1 linkages is contemplated, as part of the present invention, however, preferably the linkage is on both R_0 positions of the compounds of Formula (A).

An alternate method of preparation of the nonsymmetrical disulfide compound, wherein only one component is a compound of Formula (A), and the other half of the disulfide link is an alkyl, aryl or heteroaryl derivative, may be prepared by reaction of a sulfhydryl compound of Formula (A), with the appropriate sulfenyl halide, in an ethereal solvent to afford compounds of Formula (A) wherein one of R or R^1 is phenyl substituted with one or more [alkyl]- dithio groups, i.e. [Formula (A)-S-S-R^2], wherein R-R_2 are as defined in the above paragraph. The contemplated sulfenyl halide derivatives of alkyl, aryl, or heteroaryl groups may be optionally substituted.

The disulfide compound(s) may also be prepared from the corresponding alkyl sulfoxide compounds, such as methylsulfinyl, propylsulfinyl, iso-propylsulfinyl, wherein the alkyl can be a straight chain or branched derivative having from 1 to 9 carbon atoms, in a solvent, preferably a chlorinated one such as chloroethylene, methylene chloride or chloroform, to which is added a carboxcylic acid anhydride, such as trifluroacetic anhydride, or acetic anhydride. The Pummerer rearrangement reaction may require some heating prior to addition of an alkali metal hydroxide, such as sodium hydroxide. If acetic anhydride is used than heating is also likely to be needed during the hydroxide treatment, before addition of iodine solid (I_2), which then affords the symmetrical disulfide compound as is noted above. Mixtures of the sulfoxide compounds may be present in the solution to yield "symmetrical" compounds but with varying substituent groups on the di-heteroaryl-imidazole ring system of the present invention.

The compounds of Formula (A) are used as intermediates to form the desired 7-hydroxyl or 7 keto moiety by analogous preparation to the methods disclosed in Gallagher et al., Tetrahedron Letters, Vol. 30, No. 48, pp. 6599-6602 (1989) the entire disclosure of which is hereby incorporated by reference.

A preferred intermediate resulting from the compounds of Formula (A) as described in Gallagher et al, supra is represented by the formula (B)



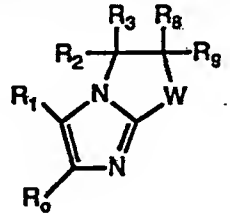
wherein R_0 to R_9 are as represented for Formula (I) and R_{10} is alkyl, phenyl, substituted phenyl, prefefably 4-nitrophenyl. Formula (B) compounds are oxidized to the corresponding 7-keto derivative or Formula (I) which is then reduced to yield the corresponding 7-hydroxy derivative of Formula (I) wherein one or R_4 or R_5 is hydroxy. Such

oxidizing agents and reducing agents are well known to those skilled in the art. Preferred oxidizing agents for use herein are Jones reagent in an organic solvent, such as acetone, THF, dioxane; potassium permanganate (buffered solution) in such solvents as ether/water, t-butanol/water, or other alcoholic solvents; and Sarretts reagent. A preferred reducing agents if sodium borohydride in a organic solvent providing a proton source, such as dichloromethane/methanol, methylene chloride, etc. or other alcoholic solvents or mixes thereof; sodium cyano borohydride which may be in a chlorinated solvents as well; lithium borohydride; superhydride (lithium triethylborohydride) in an organic solvent, such as chlorinated hydrocarbons/alcohols, etc.; and the hydride reagents, such as aluminium hydride or litihium hydride which may be in etheral or chlorinated solvents; or boron in an organic solvent.

The preparation of all the remaining compounds of Formula (I) not described herein can be readily achieved as the techniques are well known and can be carried out by one of skill in the art according to the procedures outlined above or in the Examples, infra.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

The compounds of Formula (A) are represented by the structure:



(A)

wherein

W_1 is -(CR_4R_5)-, or -(CR_4R_5)-(CR_6R_7)- ;

R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are, independently, -H or C_{1-2} alkyl; one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl; and the other of R_1 and R_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 2-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} 2-alkenyl-1-sulfinyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3}alkanamido), N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl,

dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl alkylthioalkylthio, Z, or acyloxyalkylthio;

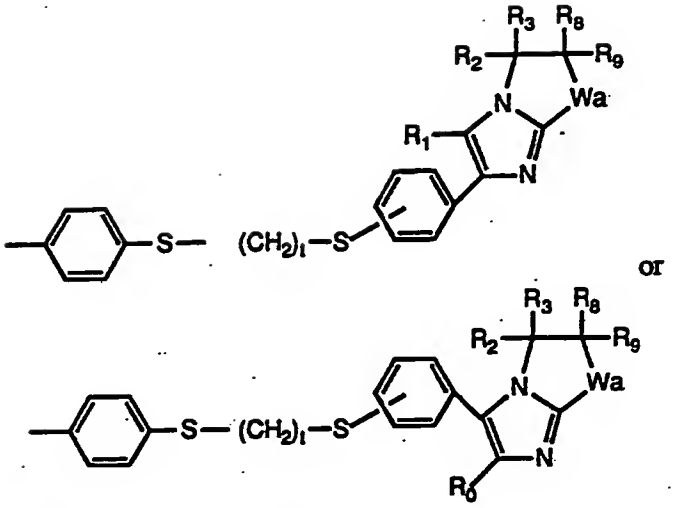
(b) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, C_{1-3} alkylamino, N- (C_{1-3}alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, amino, N-pyrrolidino or N-piperidino;

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl or CF_3, and the other substituent is thiol, alkylsulfinyl, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(d) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(e) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, hydroxy, C_{1-3} alkylthio, C_{1-3} alkyl-sulfonyl, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , alkylthioalkylthio, or Z,

(f) a moiety of one of the Formulae:



or

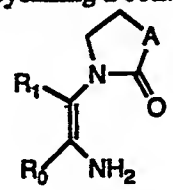
wherein t is 0 or 1;

wherein W_a, and R_1 - R_9 are as defined above;

or a pharmaceutically acceptable salt thereof.

Alternatively the compounds of Formula (A) can be preferably be prepared as outlined in the schematic below. While only a five membered pyrrole is shown the synthesis is also applicable to the six membered nitrogen containing ring. The desired R_2-R_9 alkyl substituted compounds of Formula (A) are prepared from the correspondingly R_2-R_9 substituted compounds of Formula (3).

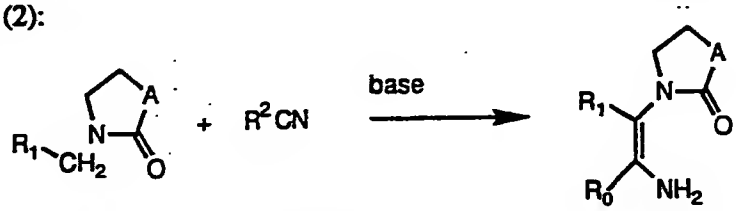
This process comprises cyclizing a compound of Formula (3):



Formula (3)

wherein A is $(CH_2)_n$ and n is 1 or 2; R_1 and R_0 are as defined for Formula (I) herein. Preferably R_0 is a phenyl substituted by a C_{1-4} alkylthio, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy.

The compounds of Formula (3) are prepared by reacting the compounds of Formula (1) and (2):



Formula (1) Formula (2) Formula (3)

Suitable bases include alkyl lithiums such as but not limited to, n-butyl lithium, potassium t-butoxide, lithium diisopropylamide, lithium hexamethylsilylazide, sodium or potassium hydride or potassium hydroxide optionally with a phase transfer catalyst such as tetraethylammonium bromide, or a suitable mixture thereof, e.g. n-butyl-lithium and potassium t-butoxide. Conveniently a compound of Formula (1) is reacted with 1 to 2 mole equivalents, preferably 1.4 to 1.7 mole equivalents of the base before treatment with a compound of Formula (2).

The reaction to form a compound of Formula (3) is in an organic solvent, such as but not limited to, THF, dialkylether, dimethylformamide, toluene, dimethylethylideneurea or tetramethylethylenediamine or a suitable mixture thereof. The reaction should be performed within a temperature range of about -80°C to about 100°C. Preferably the reaction is cooled initially and the temperature is raised to optimize the reaction time of the process.

The compounds of Formula (3) may be isolated on workup and then cyclized to a compound of the Formula (A) with a suitable base as hereinbefore described. An example of such preparation can be found in synthetic Example 3.

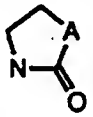
Preferably, the compound of the Formula (3) is not isolated, but is formed in situ and cyclized directly to a compound of the Formula (A) under the basic conditions of the reaction mixture. An example of such preparation can be found in synthetic Example 4.

Compounds of Formula (1) are prepared by reacting in the presence of a base a compound of Formula (4), or an acid salt thereof:

$$R_1CH_2L$$

Formula (4)

wherein R_1 is as hereinbefore defined, and L is a suitable leaving group, with a compound of Formula (5)



Formula (5)

wherein A is as defined above for Formula (3).

Examples of suitable bases include but are not limited to, potassium carbonate, sodium hydride, sodium hydroxide or lithium diisopropylamide. Suitable leaving groups (L) are well known to those skilled in the art, and include halogens, such as bromine or chloride, or a tosylate or mesylate moiety.

The reaction is performed in a solvent, preferably THF, DMF, or mixtures thereof. The reaction may optionally be performed in the presence of water in appropriate cases, where for example when using solid potassium hydroxide together with a phase transfer catalyst as the base. The reaction is conveniently performed at ambient or slightly elevated

temperatures. Preferably an aqueous solution of an acid addition salt of a compound of the Formula (4) is gradually added to a solution of a compound of the Formula (5) and the base.

The compounds of Formula (A) may be themselves used as intermediates to produce other compounds of Formula (A) and such preparations are well described in Bender et al., U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988; Bender et al., U.S. Patent Number 4,175,127, issued November 20, 1979; Bender et al., U.S. Patent Application Serial Number 07/106,199 filed on July 10, 1987; Bender et al., U.S. Patent Number 4,803,279, issued February 9, 1989, Bender et al., U.S. Patent Number 4,719,218, issued January 12, 1988; Bender et al., U.S. Patent Number 4,715,310, issued January 14, 1988 the entire disclosures of all of which are hereby incorporated by reference.

Compounds of Formula (A) wherein R_0 or R_1 is a mono- or di-substituted phenyl having a C_{1-3}alkylsulfinyl, or C_{1-3} alkenylsulfinyl; or wherein R or R^1 is a di-substituted phenyl having at least one C_{1-3}alkylsulfinyl, or C_{1-3}alkenyl-sulfinyl; or wherein R or R^1 is a mono- or di-substituted phenyl having at least one acyloxyalkylsulfinyl, alkoxyalkylsulfinyl or phenyl-sulfinyl substituent are prepared by treatment with appropriate oxidative procedures well known to those skilled in the art and additionally can be found in Bender et al., U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988; Bender et al., U.S. Patent Number 4,175,127, issued November 20, 1979; Bender et al., U.S. Patent Application Serial Number 07/106,199, filed on July 10, 1987; Bender et al., U.S. Patent Number 4,803,279, issued February 9, 1989, Bender et al., U.S. Patent Number 4,719,218, issued January 12, 1988; Bender et al., U.S. Patent Number 4,715,310, issued January 14, 1988; and in Adams et al., US Patent Application Serial Number 07/537,195, filed June 12, 1990, Attorney's Docket Number SB 14506. Preferably the oxidation is by use of potassium persulfate procedure as described in Adams et al., USSN 07/537,195, filed June 12, 1990, Attorney's Docket Number SB 14506, whose disclosure is herein incorporated by reference.

Pharmaceutically acceptable salts and their preparation are well known to those skilled in pharmaceuticals. Pharmaceutically acceptable salts of the compounds of Formula (I) to (III) which are useful in the present invention include, but are not limited to hydrochloride, hydrobromide, sulfate or phosphate salts. Preferred pharmaceutically acceptable salts of the compounds of Formula (I) can be prepared by known techniques such as the method of Bender et al., U.S. Patent 4,175,127, issued November 20, 1979 the disclosure of which is hereby incorporated by reference.

METHOD OF TREATMENT

All of the compounds of Formula (I) - (III) are useful in the methods of the subject invention, i.e. methods of treating an OPUFA disease state, specifically by inhibition of the 5-LO and CO enzymes, and the compounds of Formulas (II) and (III) are useful for

inhibiting cytokines, specifically the production of the IL-1 or TNF in an animal, including humans, in need thereof.

The oxidation of OPUFA's, specifically the arachidonic acid metabolic pathway leading to inflammatory mediators, can be controlled by the 5-LO enzyme, amongst others. The discovery that the compounds of Formula (I) are inhibitors of the 5-lipoxygenase pathway is based on the effects of the compounds of Formula (I) on the production of 5-lipoxygenase products in blood ex vivo and on the 5-lipoxygenase in vitro assays, some of which are described hereinafter. The 5-lipoxygenase pathway inhibitory action of the compounds of Formula (I) was confirmed by showing that they impaired the production of 5-lipoxygenase products such as leukotriene B_4 production by RBL-1 cell supernatants.

The pathophysiological role of arachidonic acid metabolites has been the focus of recent intensive studies. In addition to the well-described phlogistic activity (i.e. general inflammatory activity) of prostaglandins, the more recent description of similar activity for eicosanoids has broadened the interest in these products as mediators of inflammation. These mediators produce inflammatory conditions such as rheumatoid arthritis, osteoarthritis, bronchial inflammation, inflammatory bowel disease, ulcerative colitis, asthma, cardiovascular disorders, glaucoma, emphysema, acute respiratory distress syndrome, lupus, gout, psoriasis, dermatitis, pyresis, pain and other allergic oriented disorders such as allergic rhinitis, allergic conjunctivitis, food allergies, and uticaria.

Additional conditions such as blood platelet aggregation, and notably conditions resulting from thrombosis, including total or partial thrombosis, coronary thrombosis, phlebitis and phlebothrombosis are also implicated in the arachidonic acid pathway. Other disease states for which a 5-LO inhibitor would be useful is in the treatment of myocardial infarctions, rejection of organ transplants, tissue trauma, multiple sclerosis, atherosclerosis, vasculitis, glomerulo-nephritis, and immune complex disease, as well as use in the optical areas, particularly for general inflammation of the corneal anterior and posterior segments due to disease or surgery, such as post surgical inflammation or uveitis.

It has also been discovered that the compounds of Formula (I) are useful for treating disease states mediated by the cyclooxygenase pathway metabolism of arachidonic acid in an animal, including humans, in need thereof. The discovery that the compounds of Formula (I) are inhibitors of cyclooxygenase products is based upon the effects of the compounds of Formula (I) on the production of the PGE_2 products, and the human monocyte data, the assays of which are described herein.

The disease states associated with the CO metabolic pathway are typically those considered for the non-steroidal antiinflammatory drugs (nsaids), whose primary mode of action is by CO inhibition. The primary diseases of interest, but not limited thereto, are the various arthritic conditions, pyresis and pain.

Interleukin-1 (IL-1) has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

The discovery that the compounds of Formulas (II) and (III) are inhibitors of cytokines, specifically IL-1 is based upon the effects of the compounds of Formulas (II) and (III) on the production of the IL-1 in vitro, on the human monocyte, the assays of which are described herein.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

The discovery of a compound which specifically inhibits TNF production will not only contribute to the understanding of how this molecule is synthesized, processed and secreted, but will also provide a therapeutic approach for diseases in which excessive or unregulated TNF production is implicated.

Excessive or unregulated TNF production is implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity

is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, et al., Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells. Additional studies have identified TNF-α as a common factor in the activation of HIV in vitro and has provided a clear mechanism of action via the nuclear factor κB, a nuclear regulatory protein found in the cytoplasm of cells (Osborn, et al., PNAS (86) 2336-2340). This evidence suggests that a reduction of TNF synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

TNF also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin. TNF also has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells.

TNF is also believed to be an important mediator of many other inflammatory states or diseases. Therefore, inhibitors of TNF production would have utility in any inflammatory state or disease in which abnormal levels of TNF are produced. Abnormal levels of TNF constitute levels of 1) free (not cell bound) TNF, greater than or equal to 1 picogram per ml; 2) any cell associated TNF; or 3) the presence of TNF mRNA above basal levels in cells or tissues in which TNF is produced. In addition, the present invention attributes many biological disease states noted herein to IL-1 activity. These disease states are also considered appropriate disease states of TNF activity and hence compounds of Formulas (II) and (III) are also useful in their treatment as well, and should not be considered solely a limitation to IL-1 activity alone.

It has also been discovered that the compounds of Formulas (II) and (III) are useful for treating disease states mediated by the cytokine TNF in an animal, including mammals, in need thereof. The discovery that the compounds of Formulas (II) and (III) are inhibitors of cytokines, specifically TNF is based upon the effects of the compounds of Formulas (II) and (III) on the production of the TNF in - vitro, on the human monocyte, and the assays of which are described herein.

PHARMACEUTICAL COMPOSITIONS

This invention further relates to the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of prophylactically or therapeutically, any disease state in an animal, including humans, which is caused by or exacerbated by OPUFA metabolizing enzymes, such as 5-LO or CO.

This invention further relates to the use of a compound of Formulas (II) and (III), or pharmaceutically acceptable salts thereof in the manufacture of a medicament for the treatment of prophylactically or therapeutically, any disease state in an animal, including humans, which is exacerbated or caused by excessive or unregulated IL-1, or TNF production.

This invention also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formulas (I) to (III) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) are administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay

material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

To obtain a stable water soluble dose form of an insoluble Formula (I) compound, a pharmaceutically acceptable salt of the Formula (I) compound is dissolved in an aqueous solution of an organic or inorganic acid, such as a 0.3 M solution of succinic acid or citric acid.

As the compounds of Formulas (Ia), (II) and (III) are but a subgenus of the compounds of Formula (I) all applicable dosage ranges, and formulations, etc. apply to the compounds of Formula (II) and (III) unless indicated differently.

The compounds of Formula (I) may be administered topically. Thus, the compounds of Formula (I) may be administered topically in the treatment or prophylaxis of inflammation in an animal, including man and other mammals, and may be used in the relief or prophylaxis of 5-lipoxygenase pathway mediated diseases such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The amount of a compound of Formula (I), for all methods of use disclosed herein, required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the inflammatory condition, whether eicosanoid or cytokine mediated, and the animal undergoing treatment, and is ultimately at the discretion of the physician. A suitable, topical, anti-inflammatory dose of an active ingredient, i.e., a compound of Formula (I) is 0.1 mg to 150 mg, administered one to four, preferably two or three times daily.

By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by

weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural

gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The methods of the subject invention may be carried out by delivering the monokine activity interfering agent parenterally. The term 'parenteral' as used herein includes intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formulas (I) to (III), the daily oral dosage regimen will preferably be from about .1 to about 80 mg/kilogram of total body weight, preferably from about .5 to 30 mg/kg, more preferably from about 1mg to 15mg. The daily parenteral dosage regimen will preferably be from about .1 to about 80 mg per kilogram (kg) of total body weight, preferably from about .5 to about 30 mg/kg, and more preferably from about 1mg to 15mg/kg.

The compounds of Formula (I) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The preferred daily dosage amount of a compound of Formula (I) administered by inhalation for all methods disclosed herein, is from about .01 mg/kg to about 1 mg/kg per day.

It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables.

It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques.

It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

EXAMPLE A

Inhibitory Effect of compounds of Formula (I) on
in vitro IL-1 Production by Human Monocytes

The effects of compounds of Formula (I) on the in vitro production of IL-1 by human monocytes was examined using the following protocol.

Bacterial lipopolysaccharide (LPS) was used to induce IL-1 production by human peripheral blood monocytes. IL-1 activity was measured by its ability to stimulate a Interleukin 2 (IL-2) producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore, according to the method of Simon et al., J. Immunol. Methods, 84, 85, (1985). Human peripheral blood monocytes were isolated and purified from either fresh blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta et al., J. Immunol., 132, 936 (1984). 1 X 10^6 of such monocytes were plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle washing. Test compounds were then added to the cells for 1 hour (hr) before the addition of lipopolysaccharide (50 ng/ml), and the cultures were incubated at 37°C for an additional 24 hours. At the end of the incubation period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were immediately assayed for IL-1 biological activity in the manner described above, as well as for prostaglandin and/or leukotriene concentrations by radioimmunoassay.

The results indicated that human peripheral blood monocytes are exquisitely sensitive to bacterial endotoxin. Nanogram or even picogram quantities of LPS stimulated high levels of IL-1 production as well as prostaglandin production; however, little, if any, leukotriene was detected in such supernatants. These observations are consistent with previous reports [(See, Humes et al., J. Biol. Chem., 257, 1591 (1982)].

The results of the effects of compounds of Formula (I) on the in vitro IL-1 production by human monocytes is reported in Table 1. As shown in Table 1, compounds of Formula (I) are potent inhibitors of in vitro IL-1 production by human monocytes. The exact mechanism by which any compound of Formula (I) inhibits in vitro IL-1 production by monocytes is not presently known. This inhibitory activity does not seem to correlate with the property of any of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition since other nonsteroidal antiinflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity do not inhibit IL-1 production at nontoxic doses. Furthermore, the ability of a compound to inhibit production of prostaglandin and/or leukotriene synthesis does not mean that it will necessarily also inhibit IL-1 production.

Based on the widely held belief of the role of unmodulated (i.e., excessive) in vivo IL-1 production in causing or aggravating inflammatory responses and other disease states (see, e.g., Fontana et al., supra; Wood et al., supra; Akejima and Dinarello, supra; Habicht and Beck, supra; Chesque et al., supra; Benjamin et al., supra; and Dinarello, supra), and based on the fact that compounds of Formula (II) inhibit in vitro IL-1 production by human macrophages and/or monocytes (see, Table 1), the compounds of Formula (II) to (III) will inhibit the in vivo IL-1 production by monocytes and/or macrophages in a human in need thereof when used according to the method of the subject invention.

UTILITY EXAMPLE B

Inhibitory Effect of compounds of Formula (I) on in vitro TNF production by Human Monocytes

Section I: Assay set-up

The effects of compounds of Formula (I) on the in vitro production of TNF by human monocytes was examined using the following protocol.

Human peripheral blood monocytes were isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. et al., J. Immunol., 132(2):936 (1984). The monocytes were plated at a density of 1 X 10^6 cells/ml medium/well in 24-well multi-dishes. The cells were allowed to adhere for 1 hour after which time the supernatant was aspirated and 1 ml fresh medium (RPMI-1640 (Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum and penicillin and streptomycin at 10 units/ml was added. The cells were incubated for 45 minutes in the presence or absence of test compounds at 1nM-10uM dose ranges (compounds were solubilized in Dimethyl-sulfoxide/Ethanol such that the final solvent concentration in the culture medium was 0.5% Dimethyl sulfoxide/0.5% Ethanol). Bacterial lipopolysaccharide (E. coli 055:B5 [LPS] from Sigma Chemicals Co.) was then added at 100 ng/ml in 10 ml Phosphate Buffered Saline (PBS) and cultures incubated for 16-18 hours at 37°C in a 5% CO_2 incubator. At the end of the incubation period, culture supernatants were removed from the cells, centrifuged at 3000 revolutions per minute (rpm) to remove cell debris and .05 ml of the supernatant assayed for TNF activity using the radioimmunoassay described below.

Section II: Radioimmunoassay procedure for TNF activity

The assay buffer consisted of 0.01M $NaPO_4$, 0.15M NaCl, 0.025M EDTA and 0.1% sodium azide at pH 7.4. Human recombinant TNF (rhTNF) obtained using the procedure of Chen et al., Nature, 330:581-583 (1987) was iodinated by a modified Chloramine-T method described in Section III below. To samples (50 µl culture supernatants) or rhTNF standards, a 1/9000 dilution of polyclonal rabbit anti-rhTNF (Genzyme, Boston, MA) and 8000 cpm of ^{125}I-TNF was added in a final volume of 400 µl buffer and incubated overnight (18 hours) at

4°C. Normal rabbit serum and goat anti-rabbit IgG (Calbiochem) were titrated against each other for maximum precipitation of the anti-rhTNF. The appropriate dilutions of carrier normal rabbit serum (1/200), goat anti-rabbit IgG (1/4) and 25 Units heparin (Calbiochem) were allowed to precipitate and 200 µl of this complex was added per assay tube and incubated overnight at 4°C. Tubes were centrifuged for 30 minutes at 2000 rpm, supernatants were carefully aspirated, and radioactivity associated with the pellets measured in a Beckman Gamma 5500 counter. The logit-log linear transformation curve was used for the calculations. The concentrations of TNF in the samples was read of a standard curve of rhTNF that was linear in the 157 to 20,000 pg/ml range.

Section III: Radioiodination of rhTNF

Iodination of rhTNF was performed using a modified chloramine-T method of Frolik et al., J. Biol. Chem., 259:10995-11000 (1984). Briefly, 5 mg of rhTNF in 5 ml of 20MM Tris ph 7.5, was diluted with 15 ml of 0.5M KPO_4 and 10 ml of carrier free ^{125}I(100mCi/ml;ICN). To initiate the reaction, a 5ml aliquot of a 100mg/ml (aqueous) chloramine-T solution was added. After 2 minutes at room temperature, an additional 5 ml aliquot was added followed 1.5 minutes later by a final 5 ml addition of chloramine-T. The reaction was stopped 1 minute later by sequential addition of 20 ml of 50mM Sodium Metabisulfite, 100 ml of 120mM Potassium Iodide and 200 ml of 1.2 mg/ml Urea. The contents were mixed and the reaction mixture was passed over a pre-packed Sephadex G-25 column (PD 10 Pharmacia), equilibrated and eluted with Phosphate Buffered Saline pH 7.4 containing 0.25% gelatin. The peak radioactivity containing fractions were pooled and stored at -20°C. Specific activity of ^{125}I-TNF was 80-100 mCi/mg protein. Biological activity of iodinated TNF was measured by the L929 cytotoxicity assay of Neale, M.L. et al., Eur. J. Can. Clin. Oncol., 25(1):133-137 (1989) and was found to be 80% that of unlabeled TNF.

Section IV: Measurement of TNF- ELISA:

Levels of TNF were also measured using a modification of the basic sandwich ELISA assay method described in Winston et al., Current Protocols in Molecular Biology, Page 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York, USA. The ELISA employed a murine monoclonal anti-human TNF antibody, described below, as the capture antibody and a polyclonal rabbit anti-human TNF, described below, as the second antibody. For detection, a peroxidase-conjugated goat anti-rabbit antibody (Boehringer Mannheim, Indianopolis, Indiana, USA, Catalog # 605222) was added followed by a substrate for peroxidase (1mg/ml orthophenylenediamine with 0.1% urea peroxide). TNF levels in samples were calculated from a standard curve generated with recombinant human TNF produced in E. Coli (obtained from SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA).

Section V: Production of anti-human TNF antibodies:

Monoclonal antibodies to human TNF were prepared from spleens of BALB/c mice immunized with recombinant human TNF using a modification of the method of Kohler and Millstein, Nature 256:495 (1975), the entire disclosure of which is hereby incorporated by reference. Polyclonal rabbit anti-human TNF antibodies were prepared by repeated immunization of New Zealand White (NZW) rabbits with recombinant human TNF emulsified in complete Freund's adjuvant (DIFCO, IL., USA).

UTILITY EXAMPLE C

In the tests used to determine activity as 5-lipoxygenase pathway inhibitors, male Balb/c mice (20-28 g), were used. All mice were obtained from Charles River Breeding Laboratories, Kingston, N.Y. Within a single experiment, mice were age matched.

Reagents were employed as follows:

Compounds of Formula (I) were used as the free base. The compounds were dissolved in acid saline. Compounds were administered by lavage at the indicated dose in a final volume of 10 ml/kg.

For in vitro experiments, compounds were dissolved at appropriate concentrations in ethanol (final concentration 1.0%) and then diluted to final concentrations using the buffers indicated in the text.

Arachidonic Acid-Induced Mouse Ear Inflammation

Arachidonic acid in acetone (2 mg/20 ml) was applied to the inner surface of the left ear. The thickness of both ears was then measured with a dial micrometer one hour after treatment, and the data were expressed as the change in thickness (10^{-3} cm) between treated and untreated ears.

Test compounds were given orally in acid/saline at the times, indicated above, prior to the topical application of arachidonic acid. The compound, 5,6-Dihydro-2-(4-Methylthiophenyl)-3-(4-pyridyl)-[7H]-pyrrolo[1,2-a]imidazole-7-ol demonstrated an ED_{50} of 22.3 mg/kg in this assay.

Assay of 5-Lipoxygenase Activities

The 5-lipoxygenase (5-LO) was isolated from extracts of RBL-1 cells. These cells were obtained from the American Type Culture Collection (#CRL 1378) and were grown at 37° with 5% CO_2 in spinner culture using Eagles essential medium (MEM) supplemented medium with 10% heat inactivated fetal calf serum. The cells were collected from culture by centrifugation at 2,000xg for 20 minutes and then washed twice with 50mM sodium phosphate (pH 7.0) that contained lmM EDTA and 0.1% gelatin. After this wash, the cells were resuspended in fresh phosphate buffer to achieve a concentration of $5X10^7$ cells/ml. This suspension was disrupted by nitrogen cavitation using the Parr bomb at 750psi for 10 minutes. The broken cells were then centrifuged at 10,000xg for 20 minutes. The supernatant was

collected and centrifuged at 100,000 xg for 60 minutes. This supernatant was collected and stored at -70°C until assayed.

The inhibition of 5-lipoxygenase activity was measured by one of two assays, the radiotracer extent assay either measured after 90 seconds at 20°C or measured according to the method of G. K. Hogaboom et al., Molecular Pharmacol. 30, 510-519 (1986) or the continuous O_2 consumption assay. The results from either assay are comparable if not identical. All compounds were dissolved in ethanol with the final concentration of ethanol being 1% in the assay.

The radiotracer extent assay examined the 5-lipoxygenase products [transLTB$_4$ (DI-HETE), 5HETE and 5HPETE] produced after a 90 second incubation at 20°C. Aliquots (40mL) of the supernatant were preincubated with the inhibitor or vehicle for 10 minutes in 25mM BisTris buffer (pH 7.0) that also contained 1mM EDTA. 1mM ATP, 50mM NaCl, 5% ethylene gylcol and 100 mg/ml of sonicated phosphatidylcholine (total volume 0.238 ml). The 5-lipoxygenase reaction was initiated by the addition of $CaCl_2$ (2mM) and 1-C14-arachidonic acid (25mM; 100,000dpm) (final volume 0.25ml). After 90 seconds, the reaction was terminated by the addition of two volumes (0.5ml) of ice chilled acetone. The sample was allowed to deproteinize on ice for 10 minutes prior to centrifuging at 1,000 xg for 10 minutes. The deproteinized supernatants were dried under argon and then redissolved in 200 mL of ethanol. These samples were then analyzed by reverse phase HPLC as described by G.K. Hogaboom et al., Molecular Pharmacol. 30: 510-519 (1986), herein incorporated by reference. The compound-mediated inhibition of 5-lipoxygenase activity is described as the concentration of compound causing a 50% inhibition of product synthesis.

The second assay for assessing inhibition of the 5-lipoxygenase activity was a continuous assay which monitored the consumption of 0_2 as the reaction progressed. The 5-lipoxygenase enzyme (200mL) was preincubated with the inhibitor or its vehicle in 25mM BisTris buffer (pH 7.0) that contained 1mM EDTA, 1mM ATP; 5mM NaCl and 5% ethylene glycol for 2 minutes at 20°C (total volume 2.99 ml). Arachidonic acid (10mM) and $CaCl_2$ (2mM) were added to start the reaction, and the decrease in 0_2 concentration followed with time using a Clark-type electrode and the Yellow Spring 0_2 monitor (type 53)(Yellow Springs, OH). The optimum velocity was calculated from the progress curves. The compound mediated inhibition of 5-lipoxygenase activity is described as the concentration of compound causing a 50% inhibition of optimum velocity for the vehicle-treated sample.

LTC-4 / PGE$_2$ Production from Human Monocytes in vitro

a) Cell Preparation: Human monocytes were prepared from leukosource packs supplied by the American Red Cross (Philadelphia,Pa). The leukosource packs were fractionated by a two-step procedure described by F. Colatta et al., J. Immunol. 132, 936 (1984), herein incorporated by reference, that uses sequential sedimentation on Ficoll followed

by sedimentation on Percoll. The monocyte fraction that results from this technique was composed of greater than 85% monocytes (with the remainder being neutrophils and lymphocytes). The monocytes (1.5 X 10^6) were placed into polypropylene tubes and used as a suspended culture. The assay buffer consisted of RPMI 1640 buffer, [Moore, G. E. et al., JAMA, 199, 519 (1967) herein incorporated by reference] 1% human AB serum, 2mM glutamine, 100 U/ml Penicillin/Streptomycin, 25 mM HEPES [4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid], and 1mM $CaCl_2$.

b) LTC_4/PGE_2 Production: Monocytes (0.9ml/tube) were dispensed into 12 X 75 mm polypropylene tubes (as a suspended culture). Compounds (100ul of a 10X stock of the compound of interest) dissolved in the assay media was added per tube (performed in duplicate). The cells were incubated for about 45 minutes at about 7°C with constant agitation in a humidified incubator. A23187 calcium ionophore (2uM final concentration) used to stimulate the cells, was added and the monocytes were incubated an additional 15 minutes. Supernatants were then collected from each tube, clarified by centrifugation, divided into two aliquots and stored at -70°C until assayed.

c) Radio-immunoassay: Supernatants were assayed for LTC_4 production and PGE_2 by radioimmunassay; which was performed using a New England Nuclear Leukotriene [^{3}H]-LTC_4 and [^{125}I]-PGE_2 RIA Kit according to the manufacturer's (New England Nuclear, Boston Massachusetts) instructions. The compound-mediated inhibition of LTC_4 is described as the concentration of compound causing a 50% inhibition of LTC_4 production.

TPA-Induced Mouse Ear Edema

The administration of 12-0-tetradecanoylphobol acetate (TPA) to mouse ears has been shown to elicit inflammation that was attributed to both lipoxygenase (LO) and cyclooxygenase (CO) products. Corticosteroids, which inhibit LO and CO products and also cytokine production, have antiedematous activity and also inhibit inflammatory cell infiltration, while CO and LO inhibitors have only any antiedematous activity.

TPA-Induced Inflammation:

TPA (12-0-tetradecanoylphobol acetate) (Sigma Chemical Co.) in acetone (4µg/20µl) was applied to the inner and outer surfaces of the left ear of BALB/c male mice. The thickness of both ears was then measured with a dial micrometer (Mitutoyo, Japan) at both 2 and 4 hours after treatment, and the data expressed as the change in thickness (10^{-3} cm) between treated and untreated ears. The application of acetone did not cause an edematous response; therefore, the difference in ear thickness represented the response to TPA. After measuring the edema, the inflamed left ears were removed and stored at -70°C until they were assayed for MPO (myeloperoxidase) activity.

The test compounds are orally administered 15 minutes before application of the TPA. The results are the mean +/- standard deviation from measurements on the 8 mice/group.

Assay of Myeloperoxidase (MPO) In Inflamed Ear Tissue:

On the day of the assay , partially thawed ear tissues were minced and then homogenized (10% w/v) with a Tissumizer homogenizer (Tekmar Co.) in 50 mM phosphage buffer (pH 6) containing 0.5% HTAB. The tissue homogenates were taken through three cycles of freeze-thaw, followed by brief sonication (10 sec.).

The method of Bradely et al., J. Invest. Derm., 78:206, 1982, was used with the modifications described herein. The appearance of a colored product from the MPO-dependent reaction of o-dianisdine (0.167 mg/ml; Sigma Chemical Co.) and hydrogen peroxide (0.0005%; Sigma Chemical Co.) was measured spectrophotometrically at 460nm. Supernatant MPO activity was quantified kinetically (change in absorbance measured over 3 min, sampled at 15 sec intervals) using a Beckman DU-7 spectrophotometer and a Kinetics Analysis package (Beckman Instruments, Inc.). One unit of MPO activity is defined as that degrading one micromole of peroxide per minute at 25°C.

Results:

The compound, 5,6-Dihydro-2-(4-Methylthiophenyl)-3-(4-pyridyl)-[7H]-pyrrolo [1,2-a]imidazole-7-ol significantly reduced both the edematous response (-66%) and the inflammatory cell infiltration response (-66%) as reflected by the inhibition of MPO activity. The ED_{50} of MPO for this compound was 21.8mg/kg per os. This compound possessed significant anti-inflammatory activity in this model. The potency of this compound is surprisingly greater than would normally be expected.

TABLE I- IL-1 (IC_{50}) DATA:

COMPOUND NUMBER[a]	1	0.3
COMPOUND NUMBER[b]	2	2.2

a compound no. 1 is 5,6-dihydro -2-(4-fluorophenyl)-3-(4-pyridyl)-7-ol-5,6-dihydro-[7H]-pyrrolo[1,2-a]imidazole-7-ol.

b compound no. 2 is 5,6-Dihydro-2-(4-Methylthiophenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]imidazole-7-ol.

TABLE II TNF (IC_{50}) DATA:

COMPOUND NUMBER[a]	1	0.3
COMPOUND NUMBER[b]	2	2.0

TABLE III- LTC_4 (IC_{50}) DATA :

COMPOUND NUMBER[a]	1	2.3

COMPOUND NUMBER[b] .....2..... ...2.8

TABLE IV- 5-LO (IC_{50}) DATA :

COMPOUND NUMBER[a] .....1 .....≥100
COMPOUND NUMBER[b] .....2..... 70

TABLE V - PGE_2 DATA

COMPOUND NUMBER [a] .....1.....14
COMPOUND NUMBER[b] .....2.....2.3

SYNTHETIC EXAMPLES

EXAMPLE 1

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol

a) 5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol. To a solution of 5,6-dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol (0.85 grams (hereinafter g), 2.9 millimoles(hereinafter mmol)) in DMF (10 milliLiters (hereinafter mL)) was added sodium thiomethoxide (0.30 g, 4.4 mmol). The resulting mixture was heated at 120°C for 48 h, then allowed to cool. The mixture was concentrated under reduced pressure, and the residue was partitioned between H_2O and CH_2Cl_2. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was recrystallized twice from MeOH to provide a light tan solid (0.19 g, 20%). m.p. 229 - 230°C

^{1}H NMR ($CDCl_3$) : δ 8.59 (d, 2H); 7.40 (d, 2H); 7.19 (2 overlapping d, 4H); 6.18 (br d, 1H); 5.27 (m, 1H); 4.27 (m, 1H); 3.94 (m, 1H); 2.90 (m, 1H); 2.63 (m, 1H); 2.50 (s, 3H).

CIMS (NH_3); m/e (rel. int.) : 324 [$(M+H)^+$, 100], 308 (11).

Anal. Calc. for $C_{18}H_{17}N_3OS$: C 66.85, H 5.30, N 12.99, S 9.91; found : C 66.78, H 5.55, N 12.95, S 9.58.

EXAMPLE 2

5,6-Dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol

a) 1-{5,6-Dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-yl}-1-(4-nitrophenyl)methanol. To a solution of 5,6-dihydro-2-(4-fluorophenyl)-3-(4-

pyridinyl)-7*H*-pyrrolo[1,2-a]imidazole (15.0 g, 0.054 moles (hereinafter mol)) in CH_2Cl_2 (50 mL) at 0°C was added methoxyethoxymethyl chloride (30 mL, 0.26 mol). The resulting mixture was allowed to warm to room temperature and stirred for 1 hour (hereinafter h). Ether was added, and the mixture was decanted (3x). The residue was dissolved in EtOH (400 mL), and to this solution were added triethylamine (40 mL, 0.29 mol) and 4-nitrobenzaldehyde (15.0 g, 0.10 mol). The resulting mixture was heated at reflux for 48 h, then allowed to cool and concentrated under reduced pressure. The residue was partitioned between H_2O and CH_2Cl_2. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was triturated with EtOAc. The orange solid which formed was collected by filtration to afford the title compound (8.0 g, 34%) which was used without further purification.

b) 5,6-Dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-one. To a solution of Jones reagent (25 mL) in acetone (250 mL) was added 1-{5,6-dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-yl}-1-(4-nitrophenyl)methanol (5.0 g, 12 mmol). The resulting mixture was stirred at room temperature for 30 min, then the pH was adjusted to 7 - 8 with 2.5 N NaOH. The solid material was removed from the acetone solution by decantation and partitioned between 2.5 N NaOH and 1 : 2 CH_2Cl_2/ Et_2O. This mixture was filtered, and the layers were separated. The organic extract was combined with the acetone solution and evaporated under reduced pressure. The residue was partitioned between 2.5 N NaOH and CH_2Cl_2, and the organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was triturated with Et_2O to provide the title compound as an orange solid (1.5 g, 43%), which was used without further purification.

c) 5,6-Dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol. To a solution of 5,6-dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-one (crude product prepared above) in MeOH (15 mL) was added sodium borohydride (1.5 g, 40 mmol), and the resulting mixture was stirred at room temperature for 15 min. The mixture was concentrated under reduced pressure, and the residue was partitioned between H_2O and CH_2Cl_2. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was triturated sparingly with EtOAc and copiously with Et_2O. The solid which formed an overall yield of 0.90 g, 26% was recrystallized from MeOH to afford the title compound as a white solid.

^{1}H NMR (DMSO-d6) : 8.58 (d, 2H); 7.45 (dd, 2H); 7.36 (d, 2H); 7.16 (apparent t, 2H); 5.76 (d, 1H); 4.99 (m, 1H); 4.16 (m, 1H); 3.95 (m, 1H); 2.82 (m, 1H); 2.30 (m, 1H).
CIMS (NH_3); m/e (rel. int.) : 296 [$(M+H)^+$, 100].

EXAMPLE 3

6,7-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5*H*-pyrrolo-[1,2-a]imidazole

(A Formula (A) intermediate)

a) To a vigorously stirred suspension of potassium hydroxide (341.0g,6.09 mol) and tetraethylammonium bromide (51.2g, 0.24mol) in tetrahydrofuran (THF) 2.0 l) was added 2-pyrrolidinone (97.2 ml, 1.28 mol) at 20°C. A thick white slurry formed and the temperature rose to 27°C within 30 minutes.

The reaction mixture was stirred mechanically for a total of 100 minutes between 20-30°C before 4-picolyl chloride hydrochloride (200.0g, 1.22mol) in demineralized water (120ml) was added over 25 minutes. The temperature rose to 40°C and was not allowed to rise above this. The reaction mixture was stirred for 120 minutes after this addition and was then filtered through Celite. The reaction flask and filtered solids were washed with THF (400ml) and the washings combined with the filtrate. Any aqueous material carried over during the filtration was separated before the organic solution was concentrated to a volume of 800ml by atmospheric distillation of the THF. The solution was cooled to 20°C at which point 60-80 petrol (500ml) was added. The solution was stirred for 10 minutes when a further 500ml quantity of 60-80 petrol was added. This mixture was stirred for a further 10 minutes when a final 600ml quantity of 60-80 petrol was added. The mixture was cooled to 5°C for 16 hours before the product was isolated by filtration, washed with 60-80 petrol (400ml), and dried at 40°C, 100 mmHg for 24 hours. Hence 1-(4-picolyl)-2-pyrrolidinone 186.0g (86%) was obtained as a pale brown granular crystalline solid; m.p. 82-84°C; HPLC assay 96.1%; M^+, 176.0947. $C_{10}H_{12}N_2O$ requires 176.0950; m/z 176, (M^+), 147 (M^+ - C_2H_5), 119 (147-CO) and 903 (119 - HCN); ν maximum (KBr) 2950, 1690 (C=O), 1600, 1450, 1420, 1300 and 1280 cm^{-1}; δH(270 MHz, $CDCl_3$) 1.85 (2H, m, -$CH_2CH_2CH_2$-), 2.20 (2H, t, -$CH_2C(O)$, 3.10 (2H, t, -$CH_2CH_2NRR^1$), 4.25 (2H, s, PyCH_2-), 6.95 (2H, m, Ar(3,5)) and 8.30 (2H, m, Ar(2,6).

b) To a solution of 1-(4-picolyl)-2-pyrrolidinone (20.0g, 0.114mol) in dry THF (260ml) was added n-butyllithium (50.0ml of a 2.5 M solution in hexane 0.125mol) at 0 to -10°C. The addition required 10 minutes. Potassium tertbutoxide (12.7g, 0.114mol) in THF (65ml) was then added at 0 to 10°C over 5 minutes and the resultant golden yellow suspension stirred for 10 minutes. At this point 4-methylthiobenzonitrile (18.6g, 0.125mol) in THF (31ml) was added over 5 minutes at 0° to -10°C. When the addition was complete the reaction mixture was allowed to warm to ambient temperature over 30 minutes. After this period the reaction mixture was heated under reflux for 120 minutes and the cooled to 30°C before demineralised water (80ml) was added. The resultant mobile solution was stirred for 30 minutes and the aqueous layer then allowed 30 minutes to separate before it was removed.

The solvent was exchanged with ethyl acetate via a put and take distillation where 140ml solvent was removed and the replaced with 140ml ethyl acetate. This process was continued until the base temperature reached 77°C. A further 45ml ethyl acetate was added and the solution cooled to 50°C before 60-80 petrol (87ml) was added. The product crystallized on cooling to room temperature and after stirring for 3 hours the suspension was cooled to 0-5°C and stirred for a further 2 hours. The product was then isolated by filtration, washed with 60-80 petrol (40ml) and then dried at 40°C, 100mmHg for 24 hours. Hence 6,7-dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo [1,2-a] imidazole was obtained as a pale yellow crystalline solid; 17.6g, 50%; m.p. 172°C; HPLC assay 95.6%; δH (270MHz, CDCl3) 2.50 (3H, S, -SMe), 2.70 (2H, m, $-CH_2\underline{CH_2}$, CH_2-) 3.00 (2H, t, $-\underline{CH_2}CH_2CH_2NRR^1$), 4.05 (2H, t, $-CH_2CH_2\underline{CH_2}NRR^1$), 7.20 (2H, m, MeS Ar), 7.30 (2H, m, 3,5-Py), 7.50 (2H, m, Me S Ar) and 8.60 (2H, m, 2,6-Py).

EXAMPLE 4

6,7-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-5H-pyrrolo [1,2-a] imidazole (A Formula (A) intermediate)

a) To a solution of 1-(4-picolyl)-2-pyrrolidinone (2.01g, 11.4mmol) in THF (285ml) was added n-butyllithium (8.70ml of a 2.5M solution in hexane, 21.7mmol) at -70°C. The resultant yellow suspension was stirred for 90 minutes between -30 to -70°C before 4-methylthiobenzonitrile (2.72g, 18.3mmol) in THF (40ml) was added at -65°C. The reaction mixture was stirred with warming to room temperature over 15 minutes and was then stirred for a further 21 hours. After this time ammonia (720µl of a 35% w/w aqueous solution) was added which caused the reaction mixture to change from blood red to yellow in color. This solution was stirred for 30 minutes before the solvent was removed in vacuo and the residue chromatographed on silica gel using ethyl acetate: triethylamine - 96:4 as eltuant. Hence Z-1-amino-1-(4-methylthiophenyl)-2-(4-pyridyl)-2-(1-(2-pyrrolidinoyl))ethene (1.2g, 32%) was obtained as a free flowing yellow powder, m.p. 220-222°C (from ethyl acetate) M^+ 325.1271. $C_{18}H_{19}N_3OS$ requires 325.1249. ν maximum (nujol mull) 3500-3300 (N-H), 1669 (C-O), 1632 (C-C) and 1566 cm^{-1}; δH (270 MHz, d6-DMSO) 2.10 (2H, m, $-CH_2\underline{CH_2}CH_2$-), 2.40 (2H, t, $-\underline{CH_2}CH_2CH_2C(O)$-), 2.50 (3H, s, -SMe), 3.50 (2H, t, $-CH_2CH_2\underline{CH_2}C(O)$-), 5.70 (2H, s, -NH2), 6.50 (2H, m, 3,5-Py), 7.25 (4H, m, MeS Ar) and 8.05 (2H, m, 2,6-Py); m/z 325(M^+), 308 (M-NH_3), 268 (M-C_3H_5O) and 150 (C_8H_8NS).

b) To a suspension of Z-1-amino-1-(4-methylthiophenyl)-2-(4-pyridyl)-2-{1-(2-pyrrolidinoyl)}ethene (114mg, 0.351mmol) in THF (8.8ml) was added n-butyllithium (249µl of a 2.5M solution in hexane, 0.491mmol) at -40°C. The resultant dark red solution was allowed to warm to room temperature over 30 minutes and was then stirred at this temperature for 19 hours. After this time the color changed to light yellow. At this point the reaction mixture was assayed by HPLC and found to contain the title compound 88mg, 82%.

EXAMPLE 5

2-(4-fluorophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo-[1,2-a]imidazole

(A Formula (A) intermediate)

To a solution of 1-(4-picolyl)-2-pyrrolidinone (56mg, 0.318mmol) in dry THF (8ml) was added n-butyllithium (472µl of a 1.0M solution in hexane, 0.477mmol) at -80°C. The resultant cloudy bright yellow solution was stirred between -50 to -80°C for 50 minutes before p-fluorobenzonitrile (61mg, 0.8097mmol) was added in THF 93ml) at -80°C. The reaction mixture was then allowed to warm to room temperature when it became dark red. It was stirred for 18 hours before the solvent was removed in vacuo and the residue chromatographed on silica gel using ethyl acetate:methanol - 4:1 as eluant. Hence the title compound was obtained (7mg, 7%).

EXAMPLE 6

2-(4-Bromophenyl)-6,7-dihydro-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole

(A Formula (A) intermediate)

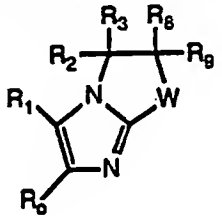
To a solution of 1-(4-picolyl)-2-pyrrolidinone (2.66g, 15.1mmol) in dry THF (76ml) was added n-butyllithium (7.26ml of a 2.5M solution in hexane, 18.1mmol) at -40°C. A solution of potassium tert butoxide (1.69g, 15.1mmol) in THF (8.5ml) was then added and the resultant golden yellow suspension stirred at -40°C for 10 minutes. At this point a solution of 4-bromobenzonitrile (5.50g, 30.2mmol) in THF (50ml) was added at -40°C and the reaction mixture then allowed to warm to room temperature. After stirring for 18 hours the reaction mixture was concentrated to dryness and the residue chromatographed on silica gel using ethyl acetate:methanol - 5:1 as eluant. Hence the title compound was obtained as a yellow crystalline solid (0.71g, 14%); M^+ 339.0371. $C_{17}H_{14}N_3{}^{79}Br$ requires 339.0371 M^+ 341.0387. $C_{17}H_{14}N_3{}^{81}Br$ requires 341.0351. δH (270MHz, $CDCl_3$) 2.65 (2H, m, -CH_2,CH_2CH_2-), 3.00 (2H, t, -$CH_2CH_2CH_2NRR'$), 4.00 (2H, t, -$CH_2CH_2CH_2NRR'$), 7.25 (2H, m, 3,5-Py), 7.40 (4H, m, Br-Ar) and 8.60 (2H, m, 2,6-Py); m/z 339 (M^+), 341 (M^+) 259 (M-HBr), 310 (M-C_2H_5) and 312 (M-C_2H_5).

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The

embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of Formula (I) as represented by the structure:



(I)

wherein

W is -(CR_4R_5)-, or -(CR_4R_5)-(CR_6R_7)- ;

R_4 and R_5 together are oxo; or one of R_4 and R_5 is OH and the other of R_4 and R_5 is hydrogen;

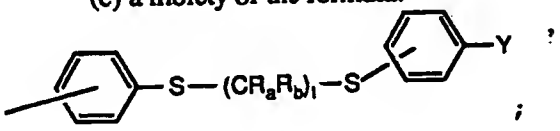
R_2, R_3, R_6, R_7, R_8, and R_9 are hydrogen; or one or two of R_2, R_3, R_6, R_7, R_8 and R_9 are independently hydrogen or C_{1-2}alkyl;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl; and the other of R_1 and R_0 is

(a) phenyl;

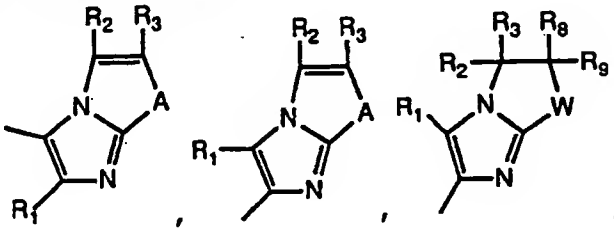
(b) mono- or di-substituted phenyl wherein the substituents are selected, independently, from C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, aryloxy, heteroaryloxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 2-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} 2-alkenyl-1-sulfinyl, arylthio, arylsulfinyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3}alkanamido), N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, acyloxyalkylsulfinyl, acyloxyalkylthio or Z; or

(c) a moiety of the formula:

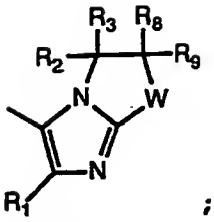


;

wherein Y is selected from



, or



wherein t is 0 or 1; W and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are as defined above;

A is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

R_a and R_b are independently selected from hydrogen, C_{1-9} alkyl, aryl or heteroaryl;

Z is $-S-(CR_aR_b)_t-S-Z_1$;

Z_1 is a functional moiety;

provided that

a) when R_1 is 4-pyridyl,W_1 is $-(CR_4R_5)-$, then R_0 is other than a 4-methoxy substituted phenyl;

b) when R_0 is pyridyl or C_{1-4}alkyl-4-pyridyl then R_1 is a phenyl substituted with other than a N-(C_{1-3} alkyl) alkanamido, or N-(C_{1-3} alkanamido);

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein R_1 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl.

3. The compound according to Claim 2 wherein R_1 is C_{1-4} alkyl-4-pyridyl and alkyl substituent is located at the 2-position of the pyridine ring.

4. The compound according to Claim 2 or 3 wherein one of R_4 or R_5 is OH.

5. The compound according to Claim 4 wherein W_1 is $-(CR_4R_5)-$.

6. The compound according to Claim 5 wherein R_0 is a mono-substituted phenyl.

7. A compound according to Claim 6 wherein R_0 is substituted by alkyl $S(O)_m$, and m is 0 or 1.

8. A compound according to Claim 7 wherein the alkyl is methyl or ethyl.

9. The compound according to Claim 8 wherein the alkyl is methyl and the substituent is in the para position.

10. The compound according to Claim 10 wherein R_2, R_3, R_8, and R_9 are hydrogen.

11. The compound according to Claim 1 which is

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one; or

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one.

12. A method of treating an OPUFA mediated disease in a mammal in need thereof, which process comprises administering to such animal an effective amount of a compound of Formula (I) according to Claim 1.

13. The method according to Claim 12 wherein the enzyme 5-lipoxygenase or cyclooxgenase is inhibited.

14. The method according to Claim 12 wherein the disease state is rheumatoid arthritis, osteoarthritis, blood platelet aggregation, thrombosis, phlebitis, phlebothrombosis, or myocardial infarctions, inflammation, bronchial inflammation, inflammatory bowel disease, ulcerative colitis, uticaria , edema, psoriasis, dermatitis, multiple sclerosis, atherosclerosis, vasculitis, glomerulo-nephritis, immune complex disease, pyresis, algesia, allergic disorders, rhinitis, allergic conjunctivitis, or food allergies.

15. The method according to Claim 12 wherein the compound is
5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;
5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;
5,6-Dihydro-2-(4-fluorophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol; or
5,6-Dihydro-2-(4-fluorophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol.

16. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier or diluent.

17. The composition according to Claim 16 wherein the compound is
5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol;
5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;
5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one;
5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-

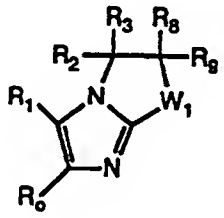
[1,2-a]imidazol-7-one; or

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one.

18. The compound 5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol.

19. The compound 5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol.

20. A method of treating a cytokine mediated disease in an animal in need of such treatment, which comprises administering to such animal an effective cytokine interfering amount of a compound of Formula (II):



(II)

wherein

W_1 is -(CR_4R_5)- ;

R_4 and R_5 together are oxo; or one of R_4 and R_5 is OH and the other is selected from H ;

R_2, R_3, R_8, and R_9 are independently hydrogen or C_{1-2} alkyl;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl provided that when R_1 or R_0 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located in the 2-position of the pyridine ring; and the other of R_1 and R_0 is

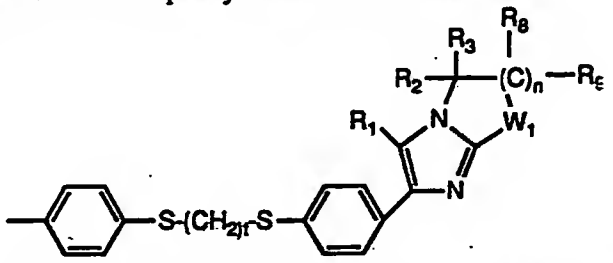
(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl or Z; or

(b) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C_{1-2} alkoxy, halo, or C_{1-4} alkyl; or

(d) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group; or

(e) monosubstituted phenyl wherein said substituent is



t is 0 or 1; W_1, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above; wherein Z is - S-S - Z_a and Z_a is a C_{1-9} alkyl or phenyl;

provided that when R_1 is 4-pyridyl,W_1 is -(CR_4R_5)-, and one of R_4 and R_5 are OH and the other is H, or together are oxo, then R_0 is other than a 4-methoxy substituted phenyl;

and the pharmaceutically acceptable salts thereof.

20. The method according to Claim 19 wherein R_2, R_3, R_6, R_7, R_8, and R_9 are hydrogen; or one or two of R_2, R_3, R_6, R_7, R_8 and R_9 are independently hydrogen or C_{1-2}alkyl;

R_1 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl;

R_0 is a monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, or halo;

or the pharmaceutically acceptable salts thereof.

21. The method of Claim 20 wherein the compound is

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol;

5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-[1,2-a]imidazol-7-one; or

5,6-Dihydro-2-(4-methylsulfinylphenyl)-3-(4-pyridinyl)-7*H*-pyrrolo-

[1,2-a]imidazol-7-one.

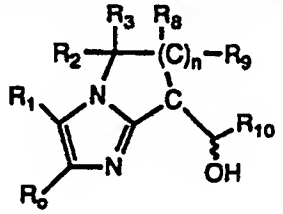
22. The method according to Claim 20 wherein the cytokine inhibited is IL-1 or TNF is inhibited.

23. The method according to Claim 20 wherein the cytokine mediated disease is septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute immune deficiency syndrome (AIDS), AIDS Related Complex (ARC) or any other disease state associated with an HIV infection, cachexia, cachexia secondary to AIDS, cachexia secondary to cancer, adult respiratory distress syndrome, asthma, chronic pulmonary inflammatory disease, Crohn's disease, ulcerative colitis, inflammatory bowel disease, bone resorption , graft vs. host reaction, acute graft rejection, or rheumatoid arthritis.

24. The method according to Claim 23 wherein the compound is 5,6-Dihydro-2-(4-methylthiophenyl)-3-(4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol or 5,6-Dihydro-2-(4-methylthiophenyl)-3-(2-methyl-4-pyridinyl)-7*H*-pyrrolo[1,2-a]imidazol-7-ol.

25. A process for producing a compound of Formula (I), according to Claim 1, which process comprises

a. Oxidizing a compound of the formula



wherein

R_2, R_3, R_4, R_5, R_6, R_7, R_8, and R_9 are, independently, -H or C_{1-2} alkyl;

n is 0 or 1;

one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl; and the other of R_1 and R_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-4} alkyl, halo, hydroxy, C_{1-4} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-3} alkylsulfonyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 2-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} 2-alkenyl-1-sulfinyl, C_{2-5} 1-alkenyl-1-sulfonyl, C_{3-5} 2-alkenyl-1-sulfonyl, C_{1-3} alkylamino, C_{1-3} dialkylamino, CF_3, N-(C_{1-3}alkanamido), N-(C_{1-3} alkyl)-N-(C_{1-3}alkanamido), N-pyrrolidino, N-piperidino, prop-2-ene-1-oxy, 2,2,2-trihaloethoxy, thiol, acylthio, dithioacyl, thiocarbamyl,

dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl alkylthioalkylthio, Z, or acyloxyalkylthio;

(b) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-3} alkoxy, halo, C_{1-4} alkyl, C_{1-3} alkylamino, N- (C_{1-3}alkyl)-N-(C_{1-3} alkanamido), C_{1-3} dialkylamino, amino, N-pyrrolidino or N-piperidino;

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkoxy, halo, C_{1-4} alkyl or CF_3, and the other substituent is thiol, alkylsulfinyl, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio, Z, or acyloxyalkylthio; or

(d) disubstituted phenyl wherein one of said substituents is amino, C_{1-3} alkylamino or C_{1-3} dialkylamino; and the other substituent is C_{1-3} alkylsulfinyl, C_{2-5} -1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1- sulfinyl, thiol, acylthio, dithioacyl, thiocarbamyl, dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl, alkylthioalkylthio,or acyloxyalkylthio; or

(e) disubstituted phenyl wherein said substituents are the same and are selected from halo, C_{1-3} alkoxy, C_{1-3} alkylamino, C_{1-3} dialkylamino, N-pyrrolidino, N-piperidino, 2,2,2-trihaloethoxy, prop-2-ene-1-oxy, hydroxy, C_{1-3} alkylthio, C_{1-3} alkyl-sulfonyl, thiol, acylthio, dithioacyl, thiocarbamyl , dithiocarbamyl, alkylcarbonylalkylthio, carbalkoxyalkylthio, alkoxycarbonylthio, alkoxythionothio, phenylthio, phenylsulfinyl, alkoxyalkylthio, alkoxyalkylsulfinyl , or alkylthioalkylthio;

to the corresponding 7-keto derivative, followed by reduction of the ketone to yield the corresponding compound of Formula (I) wherein one of R4 or R5 is hydroxy.

26. The process according to Claim 25 wherein the oxidizing reagent is Jones reagent , potassium permanganate or Sarretts reagent.

27. The process according to Claim 25 wherein the reducing agent is sodium borohydride, sodium cyano borohydride, lithium borohydride, superhydride, aluminium hydride, litihium hydride, or boron.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09417

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07D 487/00; 401/04; 471/02; 513/02; 498/02
A61K 31/505, 31/44, 31/445

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
U. S.	546/187, 271, 121; 544/281; 548/154, 218 514/258, 300, 322, 338, 339

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 5,002,941 (ADAMS ET. AL.) 26 MARCH 1991 See entire document.	1-27
A	EP, A, 1,171,739 (KYORIN PHARMACEUTICAL) 19 FEBRUARY 1986. See entire document.	1-27
A	UK, A, 2,191,196 (ROUSSEL LABORATORIES) 09 DECEMBER 1987. See entire document.	1-27
A	EP, A1, 389,352 (ADIR ET. COMPAGNIE) 26 SEPTEMBER 1990 26 SEPTEMBER 1990. See entire document.	1-27

* Special categories of cited documents: [10]

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12 MARCH 1992	27 MAR 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	AMELIA A. OWENS

Form PCT/ISA/210 (second sheet) (Rev.11-87)